RESPONSE

I. Status of the Claims

No claims have been cancelled. No claims have been amended. New claims 5-13 have been added.

Claims 1-13 are therefore presently pending in the case.

II. Support for the Newly Added Claims

Claim 5 has been added to specifically recite an isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:3. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least in claim 4 as originally filed and in Section 5.1.

Claims 6-10 have been added to specifically recite recombinant expression vectors comprising nucleic acid molecules of the present invention. Support for these claims can be found throughout the specification as originally filed, with particular support being found at page 14, lines 25-31.

Claims 11-13 have been added to specifically recite host cells comprising recombinant expression vectors of the present invention. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least from page 14, line 32 to page 15, line 5.

It will be understood that no new matter is included within the newly added claims.

III. Rejection of Claims 1-4 Under 35 U.S.C. § 101

The Action next rejects claims 1-4 under 35 U.S.C. § 101, as allegedly lacking a patentable utility. Applicants respectfully traverse.

The present invention has a number of substantial and credible utilities, not the least of which is in forensic biology, as described in the specification, at least at page 3, line 11. As described in the specification at page 17, lines 9-15, the present sequence defines two single coding single nucleotide polymorphisms, a G/A polymorphism at nucleotide position number 445 of SEQ ID NOS:1 and 3, which can result in a valine or isoleucine residue at amino acid position 149 of SEQ ID NOS:2 and 4, and a C/T polymorphism at nucleotide position number 457 of SEQ ID NOS:1 and 3, which can result

in an arginine or tryptophan residue at amino acid position 153 of SEQ ID NOS:2 and 4. As such polymorphisms are the basis for forensic analysis, which is undoubtedly a "real world" utility, the presently claimed sequence must in itself be useful. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Applicants respectfully point out that the use of the presently described polymorphisms in forensic analysis does not require the identification of a specific medical condition. The presently described polymorphisms are useful in forensic analysis exactly as they were described in the specification as originally filed - specifically, to identify individual members of the human population based on the presence or absence of one or both of the described polymorphisms. This is also not a case of a "potential" utility. Using the polymorphic markers exactly as described in the specification as originally field can definitely distinguish members of a population from one another. In the worst case scenario, each marker is useful to distinguish 50% of the population (in other words, a marker being present in half of the population). The ability to eliminate 50% of the population from a forensic analysis clearly is a real world, practical utility. Therefore, any allegation that the use of the presently described polymorphic marker is only potentially useful would be without merit, and would not support the alleged lack of utility.

Applicants further point out that not all nucleic acids contain polymorphic markers. In fact, the basis for forensic analysis is the fact that such polymorphic markers are not present in all other nucleic acids, but in fact specific and unique to only a certain subset of the population. Until a polymorphic marker is actually described it cannot be used in forensic analysis. Put another way, simply because there is a likelihood, even a significant likelihood, that a particular nucleic acid sequence will contain a polymorphism and thus be useful in forensic analysis, until such a polymorphism is actually identified and described, such a likelihood is meaningless. Additionally, Applicants point out that the requirement for a specific utility, which is the proper standard for utility under 35 U.S.C. § 101, should not be confused with the requirement for a unique utility, which is clearly an improper standard. As clearly set forth by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Just because other, or even more useful, polymorphic sequences from the human genome have been described would not mean that the use of the presently described polymorphic marker for forensic analysis is not a specific utility. If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer, just to name a few particular examples, because the utility of each of these compositions is applicable to the broad class in which each of these compositions falls: all batteries have the same utility, specifically to provide electrical power; all automobile tires have the same utility, specifically for use on automobiles; all golf balls and golf clubs have the same utility, specifically for use in the game of golf; and all cancer treatments have the same utility, specifically, to treat cancer. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions nearly every week. Furthermore, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Furthermore, as the presently described polymorphisms are a part of the family of polymorphisms that have a well established utility, the Federal Circuit's holding in *In re Brana*, (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*") is directly on point. In *Brana*, the Federal Circuit admonished the Patent and Trademark Office for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted, emphasis added. As set forth above, the present polymorphisms are useful in forensic analysis exactly as described in the specification as originally filed, without the need for any further research. Even if the use of these polymorphic markers provided additional information on the percentage of particular subpopulations that contain these polymorphic markers, this would not mean that "additional research" is needed in order for these markers as described in the instant specification to be of use to forensic science. As stated above, using the polymorphic markers as described in the specification as originally field can definitely distinguish members of a population from one another. However, even if, *arguendo*, further research might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*, which clearly states, as highlighted in the quote above, that "pharmaceutical inventions, necessarily includes the expectation of further research and development" (*Brana* at 1442-1443, emphasis added). In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

It is important to note that it has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974; "*Langer*"); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA,

1971). As clearly set forth in *Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the MPEP, "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). Absent such evidence from the Examiner, as the skilled artisan would readily understand that the present polymorphic markers have utility in forensic analysis, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Although Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as yet another example of the utility of the present nucleotide sequences, the skilled artisan would readily appreciate the utility of tracking expression of the presently claimed sequence. The specification details, at least at page 6, lines 8-10, that the present nucleotide sequences have utility in assessing gene expression patterns using high-throughput DNA chips. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. As the present sequences are specific markers of human chromosome 1 (see below), and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such DNA chips. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful.

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are

many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company (Rosetta Inpharmatics) was viewed to have such "real world" value that it was acquired by large a pharmaceutical company (Merck) for significant sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, *Science* **291**:1304, 2001). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, *Science* **291**:1153, 2001). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years). Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Applicants point out that only expressed sequences can be used to track gene expression, not just any nucleic acid. Furthermore, expression profiling does not require a knowledge of the function of the particular nucleic acid on the chip - rather the gene chip indicates which DNA fragments are expressed at greater or lesser levels in two or more particular tissue types. Skilled artisans already have used and continue to use sequences such as Applicants in gene chip applications every day without any further experimentation. Applicants respectfully point out that the fact that other nucleotide sequences can be used to track gene expression would not mean that the use of Applicants' sequence to track gene expression is not a specific utility (*Carl Zeiss Stiftung v. Renishaw PLC, supra*). Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

As yet a further example of the utility of the presently claimed polynucleotide, as described in the specification at least at page 3, lines 3-5, the present nucleotide sequence has a specific utility in "the identification of protein coding sequence and mapping a unique gene to a particular chromosome". As described in the specification as originally filed at page 17, lines 16-18, the gene encoding the presently claimed sequences is present on "human chromosome 1 (see, *e.g.*, GenBank accession number

AL365208)". Alignment of SEQ ID NOS:1 and 3 with GenBank accession number AC119673 (another genomic clone from human chromosome 1) shows that the human gene corresponding to the presently claimed sequences is dispersed on 13 or 10 exons, respectively, of human chromosome 1 (alignments and first page of the GenBank report are presented in **Exhibit A**). Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 1 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence. For further evidence in support of the Applicants' position, the Examiner is requested to review, for example, section 3 of Venter *et al.* (*supra*, at pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Applicants respectfully remind the Examiner that only a minor percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The specification at page 3, lines 6-8, details that the claimed "sequences identify biologically verified exon splice junctions, as opposed to splice junctions that may have been bioinformatically predicted from genomic sequence alone". The specification also details that "sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), *etc.*, that can be used in diagnostics and pharmacogenomics" (specification at page 11, lines 21-26). Applicants respectfully submit that the practical scientific value of biologically validated, expressed, spliced, and polyadenylated mRNA sequences is readily apparent

to those skilled in the relevant biological and biochemical arts. Additionally, Applicants once again point out that the fact that other nucleotide sequences can be used to identify exon splice junctions and map this specific region of human chromosome 1 would not mean that these uses of Applicants' sequence are not specific utilities (*Carl Zeiss Stiftung v. Renishaw PLC, supra*). Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Additionally, the Examiner notes in the Action "that the polypeptides having the amino acid sequences of SEQ IDs NOs:2 and 4 share a significant degree of amino acid sequence homology with other, prior art, human metalloproteases" (Action at page 2), but that this does not confer a patentable utility to the presently claimed sequences. Applicants respectfully point out that the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. Given the homology of the presently claimed sequences to known metalloproteases, there can be no question that those skilled in the art would clearly believe that Applicants' sequence is a metalloprotease. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Rather, as set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

Finally, the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the Patent and Trademark Office ("the PTO") itself for compliance with 35 U.S.C. § 101. While Applicants are well aware of the new Utility Guidelines set forth by the USPTO, Applicants respectfully point out that the current rules and regulations regarding

the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Applicants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section IV, below), Applicants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Applicants understand that each application is examined on its own merits, Applicants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Applicants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, Applicants submit that as the presently claimed nucleic acid molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of claims 1-4 under 35 U.S.C. § 101 has been overcome, and request that the rejection be withdrawn.

IV. Rejection of Claims 1-4 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1-4 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported

by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as claims 1-4 have been shown to have "a specific, substantial, and credible utility", as detailed in section III above, the present rejection of claims 1-4 under 35 U.S.C. § 112, first paragraph, cannot stand.

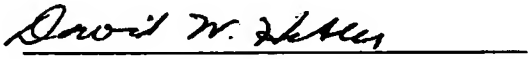
Applicants therefore request that the rejection of claims 1-4 under 35 U.S.C. § 112, first paragraph, be withdrawn.

V. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Moore have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

February 2, 2004
Date



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